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RECORD OF ORAL HEARING

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte WILLIAM S. M. WOLD, et al.

Appeal 2007-2573
Application 09/351,778
Technology Center 1600

Oral Hearing Held: March 11, 2008

Before DEMETRA J. MILLS, LORA M. GREEN, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

ON BEHALF OF THE APPELLANTS:

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The above-entitled matter came on for hearing on Tuesday, March 11, 2008, at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia, before Sean Williams, Reporter.

MS. BOBO-ALLEN: Good morning, Calendar Number 7. Appeal Number 2007-2573. Ms. De La Paz.

JUDGE MILLS: Good morning, Ms. De La Paz

MS. DE LA PAZ: Good morning.

JUDGE MILLS: We'll let you get ready. You have 20 minutes that we're going to limit you to this morning because we have a very full docket to hear.

MS. DE LA PAZ: Yes, ma'am.

JUDGE MILLS: You, you can begin when you're ready. We're particularly interested in hearing the evidence in support of your 131 declaration.

MS. DE LA PAZ: Yes, ma'am. My name is Monica De La Paz. Good morning. On the issue before the board today is whether the two declarations of the inventors are sufficient under rule 131 to establish conception of the subject matter of the appealed claims prior to the effective dates of the Henderson Patent, which is U.S. Patent 6197293 and the Little Patent which is U.S. Patent 6254862. The two declarations are designated Wold 1, which is Exhibit 4 of the Appeal Brief and Wold 2.

Now, the Examiner has argued in the supplemental answer that Appellant's evidence of conception is insufficient to meet the standard set forth in Invitrogen v. Clontech because it was not known or appreciated that the adenoviruses that are the subject of the present invention over expressed ADP or were considered as being potentially useful for treating cancer before the earliest effective dates of Henderson and Little.

Now, just as an initial matter, Appellants note that the Examiner had agreed with Appellants that prior invention under rule 131 may be

established because Appellants are not claiming the same patentable invention as Henderson or Little; and thus, there's no potential interference between the instant application and either the Henderson or Little Patents. Now, contrary to the Examiner's assertion, Appellant's evidence is indeed sufficient to demonstrate conception of the claimed invention. The Appeal Brief which we submitted sets forth art evidence of conception and during this hearing I'm going to briefly summarize only the key pieces of evidence. The evidence can be found in Exhibit 4 of the Appeal Brief. So, if you have that handy you may want to pull that up.

JUDGE LEBOVITZ: Exhibit that is in the first --

MS. DE LA PAZ: Exhibit 4, the Wold 1 Declaration. That's the first Declaration submitted by the inventors. Now, the claims there are basically two groups of claims. The claims are directed to the methods of treating cancer in an animal having a tumor, and involve administering to the tumor an adenoviral vector.

The first group of claims which are claims, are claims that explicitly recite that the vector over expresses ADP. And, the second group of claims recite particular structural variance of the adenovirus, and not explicitly the adenovirus over expresses ADP, and I'm going to break up the discussion into the group 1 claims and then the group 2 claims. So, the first group of claims are those that over express ADP.

I'm going to go to the evidence now that the inventors appreciated that the adenoviruses of their invention over express ADP. It was known in the art that ADP was a protein that was 11.6 kilodaltons encoding by the E3 region of adenovirus, and that the protein mediated cell lysis. The inventor

submitted evidence in Wold 1 that they engineered certain mutant animal viruses with deletions in the E3 region to study particularly the various function of the proteins encoded by that region. And, they constructed the two vectors; one, a designated DL-753, and another designated DL-732. These are mutant adenoviruses with a portion of the E3 region deleted other than the gene for ADP.

And, basically, what the inventors observed in their initial studies was that in cell spread assays, these vectors resulted in plaque formations that were very rapid and they were quite large. So, they conducted gel electrophoresis of the proteins encoded by those two vectors and found that they over expressed ADP. And, that evidence is set forth on Pages A-18 through A-20 of Exhibit 4, which is the Wold 1 Declaration.

JUDGE MILLS: These were replication --

MS. DE LA PAZ: So, you want to turn --

JUDGE MILLS: -- competent? They were replication competent?

MS. DE LA PAZ: They were replication competent, replication competent in the sense that they did demonstrate enlargement of the plaques on, on the cell spread assay. Replication competent as that term is used in this specification and is known in the art as it pertains to adenovirus vectors that can reproduce themselves grown in culture or in-vivo. So, yes, to the extent that they grew -- they demonstrated large plaque formation on cell spread assays, yes. So, if you turn to Page A-18 and A-19. Those show two gels, and it's actually the same gel and that shows a gel electrophoresis study that compares DL-753 to Rec700 which a wild type adenoviruses.

Now, granted the gels didn't reproduce very well, but if you look at DL-7, the DL-753 lane in A-18 there is more prominent band in the region of 11.6 kilodaltons compared to Rec700, which is the third lane from the left. And, it's even better depicted if you go to A-25. Go to Page A-25 of Exhibit 4. This is another gel. The molecular ways are shown on the far left. Rec700, which is the first lane on the left, and then DL-753, which is the third lane from the right. If you go down, you'll notice that in the region of 11.6 kilodaltons. If you look at that first arrow on the far right up from the bottom, there's a prominent band at 11.6 kilodaltons and none in the -- not a prominent band in the Rec700; the wild type sample.

Now, as far as DL-732, if you go to Page A-20, go back to Page A-20, and you'll see another example of gel electrophoresis and that compares Rec700 in the far left hand lane to DL-32, which is the fourth lane from the left. And, you'll see as well that there's a prominent band in the region of 11.6 kilodaltons. And, the legend is on Page A-18. The comparisons --

JUDGE LEBOVITZ: Why didn't they accept --

MS. DE LA PAZ: -- standard.

JUDGE LEBOVITZ: Excuse me. Why didn't the Examiner find this convincing? What was his problem with it?

MS. DE LA PAZ: The Examiner, his problem was that he felt that the inventors didn't appreciate the invention prior to the priority date, and that it wasn't until the KD vector was examined after the priority date that the inventors first appreciated --

JUDGE LEBOVITZ: Other than --

MS. DE LA PAZ: -- over expression.

JUDGE LEBOVITZ: Other than the gel evidence, is there any

written -- is appreciation required?

MS. DE LA PAZ: Well, that's a good point. In, in the Invitrogen case that case pertained to an issue of whether the inventors conceived of the invention in the context of a 102-G rejection and not conception as required for Rule 131. And so, I haven't been able to find any case law which cites to Invitrogen as showing appreciation as a requirement for conception, but I'm going to go ahead and -- I'm trying to go ahead and show you that, in deed, the inventors did appreciate that their vectors over expressed ADP.

And, let me point you to some other written evidence. If you go to, for example, Page A-14, back up, and this is shows a list of the vectors that were examined Rec700, which is shown on the top left in parenthesis after that there's a WT. That means wild type. If you go down to DL-732, which is two below Rec700, you'll see that in parenthesis after DL-732, there's ADP+++. And, behind DL-753, there's parenthesis ADP++. And, Appellants cite to this evidence as showing that, indeed, the inventors appreciated that those two vectors, which were examined and constructed over expressed ADP substantially. Not just one plus, but two plus and three plus.

And, that is also shown -- that designation regarding the ADP++ and ADP+++ is shown as well in the legends on Pages A-11 and A-12. And, you can take a look at those.

JUDGE LEBOVITZ: And, those clearly refer to --

MS. DE LA PAZ: DL-732 and DL-753; those two vectors which I mentioned that were shown to over express ADP by gel

electrophoresis. Now, there's some further evidence in Part B. If you go to Part B of this Exhibit 4, Part B basically concerns -- actually, let me step back a second. Inventors in their Declaration note in Paragraph 5 that they even confirmed ADP over expression further by conducting some amino-fluorescent studies; and those are on Pages A-21 through A-25. Go, in particular, to Page A-22, which --

JUDGE LEBOVITZ: Can I ask you a question?

MS. DE LA PAZ: Yes, certainly.

JUDGE LEBOVITZ: A-14 where you showed the pluses. Did the Examiner respond to that?

MS. DE LA PAZ: No, he did not. Page A-22; it's a busy page, but it discusses some of the results of the amino-fluorescence. If you look at Part Number 1 in the circle where it recites several lines down, R-Rec700. The results pertaining to the wild type vector are discussed, and it says about 20 to 30 percent of cells stain doe 11.6 K, which is ADP which has a molecular weight of ADP.

And, if you go down to Number 3, you'll see it says R-DL732; 70 to 80 percent stain for 11.6 K, and that's -- again this is evidence that the inventors conducted studies recognizing that here DL32 over expressed ADP relative to Rec700, the wild type vector.

JUDGE LEBOVITZ: Well, I'm, I'm not sure that's evidence of over expression. That could be evidence of that the vector was replicational competent and spreading to other cells. That's just showing a higher portion of cells have the protein in it, but it doesn't show that the protein is any different in any given cell.

MS. DE LA PAZ: Well, that's a possibility, but it's certainly

consistent with the results of the amino-fluorescence and the cell spread assay showing the larger plaques. Now, there's even more evidence of that the inventors appreciated that their vectors -- certain of their vectors over expressed ADP. If you go to Exhibit B of, of the Wold 1 Declaration and Exhibit B pertains to a grant proposal. If you go through the first several pages you'll come to the title page of the grant proposal which recites adenovirus E311.6K protein as a cell def promoting agent. Now, Page 8 -- go to Page 8 of the grant proposal. The proposal reviews earlier studies and discusses that one of its goals here is the preparation of vectors that optimize expression of ADP, if you look under Section D-1.

So, they had already constructed vectors that over expressed ADP, and they wanted to optimize it further, and, over express it further. And, this is evidence that they sought to optimize or over express ADP further in, in adenoviral vectors. So, that's additional evidence that the inventors appreciated in the context of Invitrogen that their vectors over expressed ADP, and that they recognized the significance of ADP over expression.

JUDGE MILLS: Wasn't here some disclosure in the Declarations that there was a preference for using replication defective adenoviral vectors, but a supposition that replication competent was -- would also work?

MS. DE LA PAZ: Well, the -- this proposal -- the goal here is to further elucidate the role of ADP protein as a cell death promoting agent, and so they contemplated not only vectors which were replication competent, but also evaluation of replication defective vectors. And, I'll go into that evidence soon regarding that they appreciated vectors that were replication competent.

JUDGE MILLS: Okay, you have a minute or two more if you'd like to get to the point.

MS. DE LA PAZ: Okay.

JUDGE MILLS: Get to that quickly.

MS. DE LA PAZ: Alright. So, just briefly, going onto the evidence that the vectors can be applied in cancer therapy. If you look on Page 3 of the proposal, the fourth line, inventors note that since the 11.6K protein can promote the death of adenovirus infected cells, it has the potential use as a therapeutic agent to kill cells, e.g. malignant cells in humans; so, thus, the inventors appreciated application of their vectors in cancer therapy. Also, if you look on Page 5 of the proposal, there's additional detail regarding therapeutic considerations such as limiting the -- attempts to limit the infection to the target tissue, and to minimize infection of healthy tissue, and the design of vectors to limit ADP expression to the tumor. Each of these considerations is consideration concerning therapeutic application of the vectors to treat an animal or a human with cancer.

And, the paragraph bridging Pages 9 and 10 in Part B discusses additionally animal models of human tumors and the design of, of animal studies to test whether the vectors can be applied in the treatment of cancer; so, therefore the inventors also appreciated application of their vectors in the treatment of cancer.

JUDGE MILLS: Back on Page 5 there is what I just spoke to you about that the supposition that the vectors should probably be defective, and I think the Examiner had a concern that the defective adenoviral vector was the only one that you actually had evidence for.

MS. DE LA PAZ: Well --

JUDGE GREEN: Or, that -- I don't think that that you -- that the conception was defective adenovirus. I mean, I, I think the -- I think he understood that you had a adenovirus that over expressed ADP, though you did not -- I think his argument is that you did not necessarily or appreciate that you would want such a virus in the treatment of cancer. But, going beyond that, I think his other concern was did you conceive of using a replication competent adenovirus --

MS. DE LA PAZ: Um-hum.

JUDGE GREEN: --to, to kill tumor cells.

MS. DE LA PAZ: We ask that if you look at B-4, the last paragraph -- I mean Page 4 of the Exhibit B. That paragraph discusses non-defective vectors as those where the vector can replicate in cultured human cells, and that generally have the E3 transcription unit deleted because these genes are not required for virus replication in cultured cells. And, in fact, this section discusses the KD and GZ class of vectors described in the proposal which have the E3 transcription unit deleted and replaced with the trans gene. And, Page 4 also -- let's see. On B at Page 8 discusses that the construction of such vectors is to optimize expression of 11.6K and to examine whether a non-defective vector might be useful. So, if you look particularly at Page 8 -- I don't know, first paragraph under D-1, clearly the inventors recognized that one of their goals was to examine non-defective vectors and their application in cancer therapy.

And, indeed, those early vectors I mentioned were, in fact, replication defective. So, just -- I know I have just a very short amount of time. We've also cited *In re Stempel* in our brief, which is a CCPA case which shows that the law is clear that a Rule 131 Declaration needs only to show as much as

the prior art. And, the prior art is Henderson and Little; neither of which demonstrated ADP over expression. So, to the extent that they're -- we're being required to show that, *In re Stempel* says, no that's not the case; we don't have to.

JUDGE LEBOVITZ: What about did they show replication competent or replication defective? Do you remember?

MS. DE LA PAZ: You know, I don't recall. I don't recall that they showed replication competence, but clearly we did contemplate replication competence in our vectors.

JUDGE LEBOVITZ: Just go back one second to Page 5 where it says, since we eventually hope to design a vector to promote cell death, it will be important to limit the infection; therefore, the vector should probably be defective. Would you interpret that as saying the inventors were conceiving of using a replication defective vector or were they leaving open the possibility that it could also be replication competent?

MS. DE LA PAZ: I think they, they were leaving open the possibility of it being replication competent. Another way to limit expression to the tumor is to use a tumor specific promoter which they discuss in the next sentence.

JUDGE LEBOVITZ: Okay.

MS. DE LA PAZ: And, clearly under D-1 they discuss consideration as to whether defective vectors might be useful. Just to summarize here, the Examiner didn't seem to question whether the structural claims; whether there was any question regarding conception of the structural claims, those that recite specific limitations concerning the vectors structure, but don't recite over express ADP. So, Examiner appears to

concede that the evidence of record is sufficient to support conception of those claims.

JUDGE GREEN: And you let them reject under Little and Henderson, correct?

MS. DE LA PAZ: I'm sorry.

JUDGE GREEN: They're still rejecting under Little and Henderson?

MS. DE LA PAZ: You're telling me they are?

JUDGE GREEN: I, I'm assuming. I haven't seen anything that --

MS. DE LA PAZ: We, we don't --

JUDGE GREEN: -- says that they --

MS. DE LA PAZ: We can't --

JUDGE GREEN: -- anything different.

MS. DE LA PAZ: It seems to us that he didn't -- that all the objections he raised concern the ADP over expressing claims.

JUDGE GREEN: I think back when --

MS. DE LA PAZ: That -- the arguments that we raised still apply.

JUDGE GREEN: And, I think that the Examiner's answer he did go into replication competence and some other things. So, I think his response to the supplemental Examiner's answer was a supplement to the original Examiner's answer. So, I think those could concern still --

MS. DE LA PAZ: Okay, well to the extent --

JUDGE GREEN: -- are in play.

MS. DE LA PAZ: Um-hum.

JUDGE GREEN: Yeah, I understand, but, but --

MS. DE LA PAZ: Those arguments apply then, but as far as the ADP over expression which he seemed to focus on in his response --

JUDGE GREEN: His supplemental --

MS. DE LA PAZ: -- you know, that's not germane. So, just to summarize, in accordance with Rule 131 it is respectfully submitted that Appellants have demonstrated that the inventors conceived and appreciated their invention and prior to the earliest priority date of Henderson and Little, and were diligent in reducing it to practice; therefore, it's respectfully requested that the Board reverse the rejection of the claims under 35 U.S.C. 32E as being anticipated by either Henderson or Little. And further, regarding the rejections under 103(a) based on Henderson or Little in view of Fraitag. Fraitag alone fails to teach or suggest each limitation as it's only cited as teaching combination viral therapy with radiation or chemotherapy, and not the vectors of the claimed invention. And, therefore, Appellants respectfully request that those rejections under 103(a) be reversed as well.

JUDGE MILLS: Okay, you are handling the next case also?

MS. DE LA PAZ: Yes, I am.

JUDGE MILLS: Oh okay, I was just making sure.

MS. DE LA PAZ: Okay.

JUDGE MILLS: Give me a minute to pull it up here on our screen.

MS. DE LA PAZ: Okay.

JUDGE MILLS: So, you can get organized while we --

MS. DE LA PAZ: Gather my things.

(Whereupon, the proceedings concluded.)